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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 15 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **SECOND** RfD/Peer Review Report of Cyhalothrin / Karate.

CASRN. 68085-85-8
EPA Chem. Code: 128868
Caswell No. 271F

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

TO: George LaRocca, PM 13
Insecticide-Rodenticide Branch
Registration Division (7505C)

In the meeting of the Health Effects Division RfD/Peer Review Committee on February 12, 1993 the Committee recommended that "the highest dose level tested in the mouse carcinogenicity study appears to be approaching an adequate dose for carcinogenicity testing in males based on decreased body weight gain. On the other hand, questions were raised concerning the adequacy of doses tested and the incidence of mammary tumors in females". In the mouse carcinogenicity study, the chemical was tested up to 500 ppm. The Committee requested submission of any relevant data supporting the selection of the dose levels tested in the mouse carcinogenicity study and historical control data on the mammary tumors observed in this study before a final decision could be made regarding this study. The chemical was classified, tentatively, as a "Group D" (RfD Peer Review report dated August 25, 1993).

The RfD/Peer review Committee reconvened on June 16, 1994 to reconsider the carcinogenicity issues and other questions raised by the Committee in the previous meeting. Material available for review included data evaluation records for a carcinogenicity study in mice (83-2b), a 28-day range-finding study in mice, and a chronic toxicity study in dogs (83-2b) and additional information submitted by the registrant on issues subject of this meeting.

1. Discussion of the adequacy of dose levels tested

In the registrant response, it was stated that the two-year mouse was started in 1980, before records were kept on selection of

dose levels. Therefore, the reasoning had to be constructed from the 28-day mouse study. The registrant also stated that hypertrophy of the liver was not established to be of no toxicological significance at that time. In addition, the highest dose to be tested was set on the response of the most sensitive sex.

In the 28-day range finding study, cyhalothrin was tested at 0, 5, 25, 100, 500 or 2000 ppm via dietary administration in CD-1. Twelve animals per sex per dose were used. At 2000 ppm, piloerection, abnormal gait, hunched posture, increase in respiration rate and emaciated appearance were observed. Six males and three females died during the study. Both males and females had a significant decrease in body weight gain over the treatment period when compared to controls. A decrease in food consumption was observed in both sexes during the first week and in females for the remainder of the study. Males had a slightly lower mean total white blood cell count. The differential white cell count revealed lower lymphocyte counts and higher neutrophil counts for all hematological values in males at this level. Significantly higher APDM activity and some organ weight changes were observed in both sexes. At 500 ppm, effects were minimal. Thus, from this study, it is obvious that 2000 ppm is an excessive level as evidenced by mortality.

In view of the above, the Committee concluded that the chemical was not tested at a sufficiently high dose level for carcinogenicity testing in mice.

Subsequent to the meeting, the respective branch determined that "there was not enough toxicological concern to warrant a requirement for a new carcinogenicity study in the mouse at this time. This decision was based on data from the mouse study, the 28-day range finding study in the mouse and the results from mouse and rat carcinogenicity studies conducted with similar pyrethroids" (P. Hurley memo to G. Ghali, dated Aug. 16, 1994).

2. Discussion of the incidences of mammary adenocarcinomas

In this study the chemical was tested at 0, 20, 100 and 500 ppm in CD-1 mice. Incidences of mammary adenosarcomas appeared to be increased in females of the mid-dose level (7/52, 13.5%) and high-dose level (6/52, 11.5%) . The increased incidences were statistically significant at 100 ppm ($p = 0.03$) and 500 ppm ($P = 0.04$). There was also a positive dose-related trend. However, there was a lack of a consistent dose-related response and the incidence at the mid-dose level was slightly higher than the laboratory's historical control range (2-12%, average of 17 studies of the same or longer duration performed between May 1978 and November 1980 was 7.0%). The incidence at the high-dose level was within the historical control range. The concurrent control was relatively low and was among the lowest of the historical control

range. Furthermore, there was no evidence of decreased latency or time of onset of the mammary tumors in comparison with controls.

Because of the equivocal nature of the findings, and in view of the inadequacy of the dose levels tested, the Committee concluded that the chemical should be classified as a "Group D". The Committee deferred to the respective toxicology branch the question of whether a new mouse study should be required.

3. Discussion of the NOEL/LOEL in the one-year dog study

In the meeting of February 12, 1993, the Committee decided to lower the NOEL from 0.5 mg/kg/day to 0.1 based on evidence of neurotoxicity described as slight ataxia and convulsions in some animals at 0.5 mg/kg/day and higher dose levels. Blood stains on the floor of the cage and frequency of fluid feces were also observed at this dose and higher dose levels.

After reviewing the registrant's rebuttal on this issue, the Committee reiterated their position of the February 12, 1993 meeting. It should be noted that the NOEL generated in the dog feeding study was used as basis to establish the RfD for this chemical. Consequently, the RfD should remain unchanged.

A. Individuals in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

Esther Rinde

William Sette

Rick Whiting

2. Peer Review Committee Members and associates in absentia (Signature indicates concurrence with the peer review unless otherwise stated).

George Ghali

3. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Roger Gardner

Pam Hurley

CC: Richard Schmitt
Stephanie Irene
Pam Hurley
Karl Baetcke
Roger Gardner
Pam Hurley
James Kariya
Kerry Dearfield
RfD File
Caswell File